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MELLON INSTITUTE OF INDUSTRIAL RESEARCH

University of Pittsburgh

SPECIAL REPORT

on

THE TOXICITY OF THE GLYCOLS AND THEIR DERIVATIVES

83. Chemical Burns of the Eye

Carbide & Carbon Chemicals Corporation Industrial Fellowship No. 274-4

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Report 27 of this series, issued 10-7-38, discussed the effect from 24 materials placed in the rabbit eye. Since that time about 100 additional materials have been applied and a rating system for activity in injuring the eye has been developed.

Two data on each material are desired, (1) the greatest volume of undiluted sample which can be put on the cornea without causing a chemical burn, and (2) the greatest concentration which can be applied in excess without producing a burn. A third useful datum would be the longest exposure to saturated vapors which does not cause corneal necrosis, but little work has been done upon this phase yet.

The Injury

In this study an injury is considered a chemical burn of the eye when there is necrosis (killing) of corneal tissue. Necrosis is sometimes also evident on the lids. Inflammation of the mucous membrane or injection of the scleral capillaries has not been considered a chemical burn, but merely evidence of irritation. It is usually, but not always, present simultaneously with corneal necrosis.

Corneal necrosis may involve permanent loss of sight and always affords opportunity for infection. Thus, human eyes cannot be tested and dependence must be placed upon animals. The albino rabbit is the most convenient test animal.

The mechanism of corneal necrosis appears to be irreversible coagulation or denaturation of the protein of the corneal cells. Apparently any agent coagulating or denaturing protein may cause necrosis. Acids and alkalis are the most obvious, but many neutral solvents can also act in this way. Hydrolysis of an ester to acid or alkali is not necessary for the development of necrosis. Theoretically dehydrating agents can produce a burn but none of those studied so far do so. Physical agencies such as radiation have not been considered.

Corneal necrosis is detected by applying a dye. The membranes of vigorous living cells are able to exclude the dye so that these cells do not become colored, while dead cells cannot so protect themselves and they become dyed. It is possible that cells may be so much injured that they cannot exclude the dye, but still they are alive. They may later die or regain their vigor. We believe we are justified in considering such cells to be killed, for they have lost their protective mechanism and hence are as easy prey to bacterial infection as to our dye. They are as much a menace to the health of the eye as if they had been killed. Repeated application of the dye does not injure cells sufficiently to cause them to be dyed, so our indicator cannot produce false positive reactions.

Rating System

The materials so far tested range in activity from those which do not injure when an excess (0.5 ml.) is placed in the rabbit eye, to those which produce necrosis when the minimum practical volume (0.001 ml.) is applied. Small differences in effective volume do not appear to be significant, and with this report we introduce a rating system for eye injuring potentiality by which the materials may be divided into a few grades of activity.

It would be incorrect to speak of these as grades of hazard, for they do not allow for the ease with which a material may reach the eye. That is, a volatile material is more hazardous than one of low vapor pressure but of the same grade of activity, and one of low viscosity is more hazardous than a thick fluid. It is hoped that eventually enough work may be done to allow for the latter factors and thus to be able to speak properly of grades of hazard. In the meantime, we may say that the hazard within a given activity grade appears to be directly as the vapor pressure and inversely as the viscosity.

The volumes and concentrations which have been selected to define the various grades of activity are listed below and form approximate logarithmic series.

Grade	0 -	no necrosis from	0.5 ml.	undiluted
"	1 -	" " "	0.1 ml.	"
"	2 -	" " "	0.02 ml.	"
"	3 -	" " "	0.005 ml.	"
"	4 -	" " "	0.001 ml.	"
"	5 -	necrosis from	0.001 ml.	"

Grade	0 -	no necrosis from excess of	100%	
"	A -	" " " " "	40%	solution
"	B -	" " " " "	15%	"
"	C -	" " " " "	5%	"
"	D -	" " " " "	1%	"
"	E -	" " " " "	0.1%	"
"	F -	necrosis from	0.1%	solution

Unfortunately there is no direct connection between the activity grades of a material undiluted and as a solution, so that both ratings must be considered in estimating its dangers in use. The materials so far found to be in grade 5 are distributed between grades B to E. No material has yet been found to be in a higher grade as solution than undiluted, and no material has yet been placed in Grade F, although incomplete work indicates the glyoxalidines (amine 220, etc.) may fall in this grade.

Grade 5 no doubt includes materials of several activities, ranging from those which would not produce necrosis in a volume of 0.0002 ml., down to those which would produce necrosis in a volume of 0.000001 ml. or less if any such exist. It is impossible to separate these, however, because we cannot apply less than 0.001 ml. to the eye. Distinctions between water soluble members of grade 5 can be made on the basis of the activity of solutions.

The materials which are known to have caused human eye injury of various degrees in the plant or laboratory, and which have been tested on rabbits, all fall in grade 5, and in grades C, D, and E as solutions.

Methods

Guided by previous experience, one of the volumes or concentrations listed above is delivered onto a rabbit cornea from a pipette. In the case of the two smallest volumes a specially made pipette is used, in which 0.001 ml. is equivalent to 2.5 mm. of bore. Eighteen to 24 hours later the eye is flooded with a 5 per cent aqueous solution of the sodium salt of fluorescein, flushed with physiological saline, and carefully examined for fluorescent yellow-green stained areas indicating necrosis. Such areas produced by undiluted materials are dense with sharply defined edges, indicating killing of almost every corneal cell at the point of first contact. The area of necrosis is related to the volume applied, and may be less than one square millimeter for small volumes of relatively inactive materials, or may cover the entire cornea for other materials. Acids and alkalis produce clouding of the cornea before necrosis can be demonstrated by staining. The delayed appearance of fluorescein staining is in agreement with delayed symptoms reported by human industrial victims.

When injury is from a dilute solution or from a vapor, the fluorescein stained area may be quite diffuse without sharply defined edges, indicating that scattered cells over the cornea are killed. Such staining is difficult to detect with certainty, particularly as the minimum injurious concentration is approached.

Dense necrosis heals from the edges, so that day after day the area of necrosis grows less without a diminution in density. Diffuse staining heals by growing more diffuse. Permanent opacity or spectacular scars may result on the cornea after necrosis is no longer demonstrable. In extreme cases we have produced a scar covering half the cornea, consisting of mucous membrane with a visible blood supply; and in one case we produced a thickened cone of clear corneal tissue three millimeters high. Both represent permanent loss of useful sight. Acetic anhydride was the first agent and ammonia the second. The character of final scar seems in accord with the acid (coagulating) property of the former, and the alkaline (lytic) property of the latter.

Once a rabbit eye has developed corneal necrosis, no further applications to it are made, but before this applications of different sorts are made once or twice a week to the same eye. We no longer follow healing rate on burned rabbit eyes for it has been found to vary widely between different rabbits, and to be more rapid in rabbits than in the few human cases upon which we have information. All data are based upon two eyes in agreement for each volume or concentration, near the threshold, or upon two out of three eyes tested.

Results

Results are listed alphabetically in Table 4-57 below. Following this the materials are grouped by activity grades. It will be seen that fewer volumes and concentrations are being used than formerly, to avoid a confusing number of grades of activity and to reduce a fictitious appearance of high precision in the results.

Table 4-57

Results of Corneal Necrosis Tests in the Rabbit Eye

(0.001 ml. was least, 0.5 ml. was greatest volume applied)

Material	Minimum Vol. for Necrosis ml.	Activity Grade Undiluted	Minimum Conc. for Necrosis, %	Activity Grade of Solution
Dichlorisopropyl ether	0.10	2		

Table 4-57 (continued)

Material	Minimum Vol. for Necrosis ml.	Activity Grade Undiluted	Minimum Conc. for Necrosis, %	Activity Grade of Solution
Ethyl benzene	0.10	2	-	-
2-Ethyl hexanol	0.005	4	-	-

Table 4-57 (continued)

538.

540.

<u>Interpretation</u>

Corneal necrosis is considered to represent the possibility of permanent injury to the eye, for it offers opportunity for infection, or even in the absence of infection it may heal as an opaque scar. In those human industrial cases which we know of, it has always resulted in lost working time, even when no permanent injury was done.

Some degree of industrial hazard is believed to accompany the use of any material in activity grades 4 or 5; that is, of any material producing necrosis in the rabbit eye in a volume of 0.005 ml. undiluted or less. The degree of eye hazard will vary with the viscosity of the fluid (tendency to splash into the eye) and with its vapor pressure or sublimation tendency (probability of concentrated vapors reaching the eye).

The degree of hazard to customers will of course vary with the manner of use of the material. One must consider activity both of the undiluted material and of its solutions.

It must be remembered that a material may be painful to the eye in smaller volumes or concentrations than those listed as thresholds for corneal necrosis. Such pain reactions can best be judged experimentally by studies of mucous membrane irritation (rabbit eyelid). A few such studies have been made, but they are not considered here.

<u>Treatment</u>

We have done enough animal work to be convinced that the immediate emergency treatment following accidental entry of any of these materials into the eye should be the same, and that nothing is gained by attempting to treat acid and alkali burns differently. This treatment must consist of prompt removal of the offending agent by prolonged gentle flushing with water or physiological saline. A local anesthetic salve may then be applied to make the victim comfortable. Further treatment must be in the hands of an ophthalmologist. A few minutes delay in the initial flushing may cause permanent loss of sight, so that facilities for flushing must be at the place of work. This is most simply done by providing easily accessible bubble fountains, operated by foot treadle, so a man can hold his own eye open while he flushes. An eye cup is inadequate for this flushing. After such preliminary flushing the victim should be taken to a dispensary where more thorough flushing is possible and where his pain may be relieved while he awaits examination by an opthalmologist.

At one time it was believed that instillation of milk of magnesia is a rational treatment for eye burns from acid. However, on rabbits we have shown that several brands of this preparation can themselves cause corneal necrosis, due apparently to the slow conversion of the amorphous compound to the crystal form, brucite. In the human eye we find milk of magnesia possesses no emolient properties, and is distinctly painful. It has been shown by others that attempts to neutralize acid or alkali in situ produce more severe skin burns than follow flushing, due to the locally applied heat of neutralization. For these reasons we strongly recommend against the use of milk of magnesia or any other neutralizing agent in the eye.

Acid and alkali burns cause immediate pain so the victim is warned or even forced to treat the eye at once. Some and perhaps all neutral agents causing corneal necrosis lack this warning property, and when they are splashed into the eye in small amounts or when entering as vapors the victim may have no perception of the accident until pain starts to be felt several hours later. At this time the damage has been done and flushing is of no avail, for any unreacted irritant is now inside the corneal cells. For such agents prevention alone will save the plant from lost time accidents.

Prevention

Prevention consists of avoiding splashes, ventilation to remove concentrated vapors, and as a last resort the wearing of vapor-tight goggles when volatile materials dangerous to the eye are being handled. Care must be taken with these goggles, for one accident was apparently caused by wiping fluid from the goggle rim into the eye when the goggles were removed. Of course the eyes should never be wiped with the hands when working with hazardous materials.

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